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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,471	11/04/98	ROSE-JOHN S	012627-009

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1646	17

DATE MAILED: 08/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/142,471	Rose-John
Examiner	**Group Art Unit**
Eileen B. O'Hara	1646

☒ Responsive to communication(s) filed on *Jun 19, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-9 and 11* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9 and 11* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Claims 1-9 and 11 are pending in the instant application.

Election/Restriction

2. Applicant's election of cytokine species IL-6 in Paper No. 16 is acknowledged.

Claim 5 is withdrawn as being drawn to a non-elected species.

Specification

3. Sequences are disclosed in Figures 1, 2 and 3 without the required reference to the sequence identifiers (SEQ ID NOS:). Also, the instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. This can be resolved by adding a reference to the Figures or the Brief Description of the Drawings. In addition, the primers on pages 7 and 8 need to be referred to by their particular sequence identifier. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a fusion protein comprising a cytokine and its ligand, does not reasonably provide enablement for a conjugate comprising a cytokine and its ligand that are linked by disulfide bonds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-4 encompass a conjugate comprising a cytokine receptor and its ligand linked either by a polypeptide so as to form a fusion protein, or by linking the two proteins via disulfide bonds. The instant specification discloses two fusion proteins comprising IL-6R and IL-6, identified as H-IL-6 and H-IL-6(2), and provides data that H-IL-6 stimulates the expression of haptoglobin in HepG2-IL-6 cells (which do not express IL-6R). The claims are thus enabled for the fusion protein. However, the claims also encompass a cytokine receptor and its ligand linked together by disulfide bonds. Though the specification mentions that a linker can be a disulfide bond, there is no working example of a cytokine receptor and its ligand linked by disulfide bonds. One skilled in the art may be able to insert or substitute cysteine residues in the two polypeptides and to design denaturation and renaturation protocols in order for disulfide bonds to form between them with minimal experimentation, however, to do so with the expectation that they would retain function would require undue experimentation. It is not predictable where cysteine residues could be inserted or substituted in proteins, in order to form disulfide bridges between two proteins, and have them still retain activity. A protein's activity is dependent on its

conformation, and changing even a single amino acid can render a protein inactive, temperature sensitive or unable to form necessary interactions with other proteins or molecules. It is not disclosed and not predictable from the limited teachings of the prior art and specification if a conjugate comprising a cytokine receptor and its ligand linked by disulfide bonds and retaining function could be synthesized, even for a single cytokine-receptor pair, much less for the scope encompassed by the claims. Because of the unpredictability of the art and lack of guidance in the specification, it would require undue experimentation to make and use the conjugate as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 6-9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5.1 Claim 1 (and dependent claims 2-9 and 11) are vague and indefinite because claim 1 recites " a disulfide bridge formed by two polypeptides", and it is not clear if the two polypeptides are the receptor and ligand or two different polypeptides. This rejection would be obviated by inserting "the" between "by" and "two" or replacing "by" with "between the".

5.2 Claim 1 is also indefinite because as written it encompasses a linker that is a disulfide bridge formed by "a polypeptide", and in order to link two polypeptides by a disulfide bridge both polypeptides have to form the bridge. It is not clear if the linker is meant to be a disulfide bridge, or if the linker can be a different polypeptide that links the receptor and cytokine polypeptides.

5.3 Claims 2 and 3 are indefinite because they recite "its subunit", and it is not clear or defined what the subunit is.

5.4 Claim 11 is indefinite because it is a method claim, but is not written with the different methods steps clearly recited. An acceptable method claim must contain three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved. Claim 11 merely recites "using", which is not a method step.

5.5 Claim 11 is also indefinite because it comprises influencing the interaction between proteins by using a protein conjugate along with the DNA coding for said conjugate, and it is not clear how using both the conjugate and the DNA encoding it would together influence protein interactions, nor how the DNA and protein are to be so "used".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4, 6-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sui et al, PNAS, Vol. 92, March 1995, and further in view of Wong et al, WO 96/04314, Feb. 15, 1996 (both cited in IDS).

Claims 1-4, 6-9 and 11 encompass a conjugate comprising a cytokine and its ligand linked to each other via a disulfide bridge or a polypeptide linker, a plasmid comprising DNA encoding a such a fusion polypeptide, a transformant comprising the plasmid, and a method for influencing the interaction between proteins comprising using the conjugate.

Sui et al teach that a complex comprising soluble IL-6 receptor and IL-6 expands hemopoietic progenitor cells and CD34+ cells by initiating gp130 and c-Kit signaling. Sui et al differs from the claimed invention in that they do not teach that the receptor and the ligand in the IL-6R/IL-6 complex are bound by either disulfide bridges or by a polypeptide linker to form a fusion protein.

Wong et al teach expression vectors encoding MHC fusion complexes that contain an MHC molecule and a presenting peptide covalently linked to the MHC protein, and state that "It would thus be desirable to have MHC molecules that contain an antigenic peptide for modulation of the activity of a T cell receptor." (Page 3, lines 17-18). Wong et al further teach that covalently linking the presenting peptide to the MHC peptide provides a number of significant advantages, one of which is avoidance of costly purification steps typically associated with

preparation of recombinant proteins(page 4, lines 26-29), and in reducing the complex to a single molecule, yields and stability of the molecules may be enhanced (page 6, lines 16-18), and that the linker sequence should allow effective positioning of the presenting peptide with respect to the MHC molecule binding groove so that the presenting peptide can modulate the activity of a T cell receptor (page 5, lines 21-23).

Given the teachings of Sui et al that it would be desirable to administer a complex of IL-6 receptor and IL-6 to expand hemopoietic progenitor cells, and the teachings of Wong et al that it would be more efficient and/or effective to administer two different proteins together as a fusion protein than separately, it would have been *prima facie* obvious to one of skill in the art of cytokines and their receptors at the time of the invention to use the method of making a fusion protein of Wong using the IL-6R/IL-6 complex of Sui, in order to more efficiently make and administer the complex, as suggested by Wong. Given the state of the art of making fusion proteins, one would have had a high expectation of success that a IL-6R/IL-6 complex could be made that would retain biological function.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D

Patent Examiner

LORRAINE SPECTOR
PRIMARY EXAMINER